Claims

1. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in cholesterol-lowering therapy.

2. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of hypercholesterolaemia, hyperlipoproteinaemia and/or hypertriglyceridaemia.

3. The use as claimed in Claim 1 or Claim 2, wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

4. The use as claimed in any one of the preceding claims, wherein the thrombin inhibitor is melagatran.

5. The use as claimed in Claim 4, wherein the derivative of melagatran is a prodrug of melagatran.

6. The use as claimed in Claim 5, wherein the prodrug is of the formula

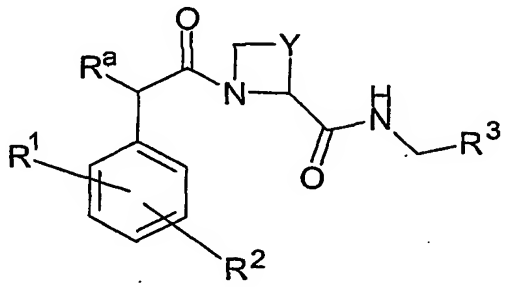
$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}(S)Aze\text{-}Pab\text{-}OH,$$

wherein R^1 represents linear or branched $C_{1\text{-}6}$ alkyl and the OH group replaces one of the amidino hydrogens in Pab.

7. The use as claimed in Claim 6, wherein R^1 represents methyl, ethyl or propyl.

8. The use as claimed in Claim 7, wherein R^1 represents ethyl.

9. The use as claimed in any one of Claims 1 to 3, wherein the thrombin inhibitor is of formula I,



I

wherein

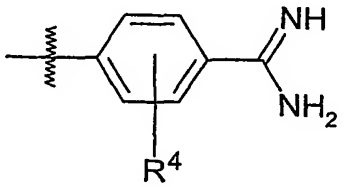
R^a represents -OH or $-CH_2OH$;

R^1 represents at least one optional halo substituent;

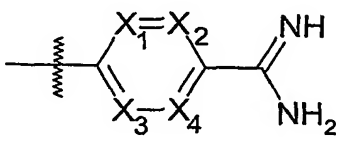
R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents $-CH_2-$ or $-(CH_2)_2-$; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

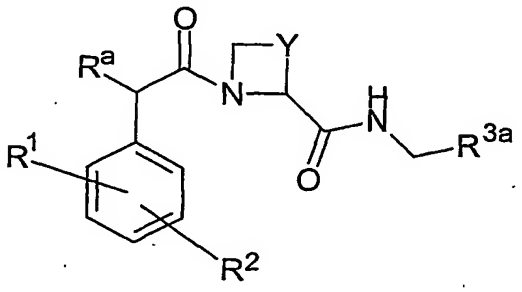
R^4 represents H or one or more fluoro substituents; and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-.

10. The use as claimed in Claim 9, wherein the thrombin inhibitor is:
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab;
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF); or
Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab.

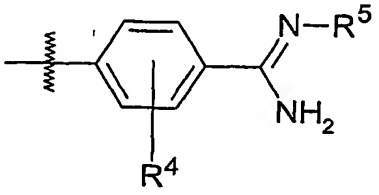
11. The use as claimed in Claim 9 or Claim 10, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

12. The use as claimed in Claim 11, wherein the prodrug is of formula Ia,

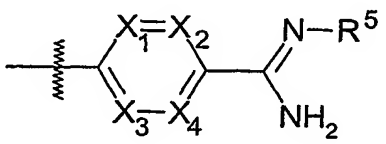


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a, R^1, R^2, Y, R^4, X_1, X_2, X_3 and X_4 are as defined in Claim 9.

13. The use as claimed in Claim 12, wherein the prodrug is:
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe);
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe); or
Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe).

14. A cholesterol-lowering therapy method, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such therapy.

15. A method of treatment of hypercholesterolaemia, hyperlipoproteinaemia and/or hypertriglyceridaemia, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

16. The method as claimed in Claim 14 or Claim 15 wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

17. The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is melagatran.

18. The method as claimed in Claim 17, wherein the derivative of melagatran is a prodrug of melagatran.

19. The method as claimed in Claim 18, wherein the prodrug is of the formula

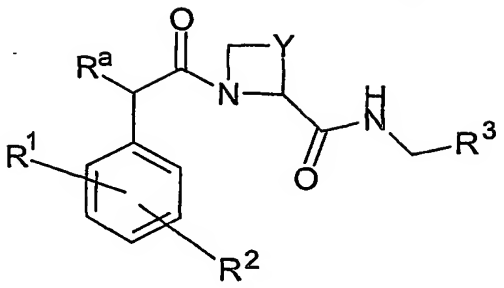
$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}(S)Aze\text{-}Pab\text{-}OH,$$

wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab.

20. The method as claimed in Claim 19, wherein R^1 represents methyl, ethyl or propyl.

21. The method as claimed in Claim 20, wherein R^1 represents ethyl.

22. The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is of formula I,



wherein

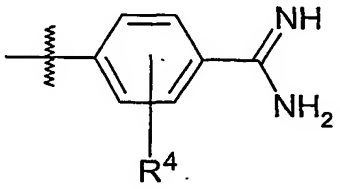
R^a represents -OH or $-CH_2OH$;

R^1 represents at least one optional halo substituent;

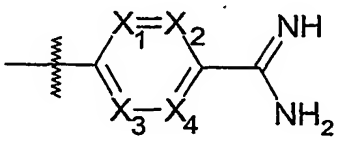
R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents $-CH_2-$ or $-(CH_2)_2-$; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

R^4 represents H or one or more fluoro substituents; and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-.

23. The method as claimed in Claim 22, wherein the thrombin inhibitor is:

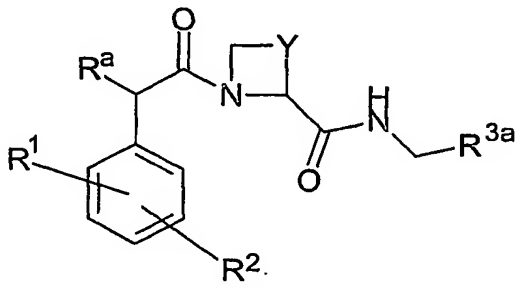
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab;

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF); or

Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab.

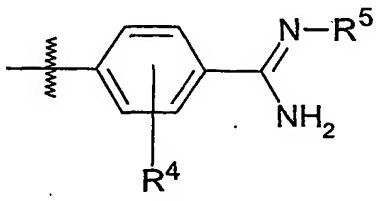
24. The method as claimed in Claim 22 or Claim 23, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

25. The method as claimed in Claim 24, wherein the prodrug is of formula Ia,

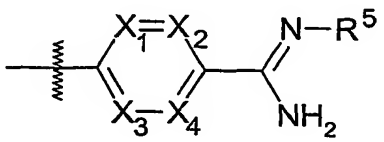


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts

of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a, R^1, R^2, Y, R^4, X_1, X_2, X_3 and X_4 are as defined in Claim 22.

26. The method as claimed in Claim 25, wherein the prodrug is:

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe);

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe); or

Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe).

27. A combination product comprising:

(A) a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof; and

(B) another cholesterol-lowering, or lipid-lowering/modifying, therapeutic agent,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

28. A combination product as claimed in Claim 27, which comprises a pharmaceutical formulation including the thrombin inhibitor or derivative, the other therapeutic agent and a pharmaceutically-acceptable adjuvant, diluent or carrier.

29. A combination product as claimed in Claim 27, which comprises a kit of parts comprising components:

(a) a pharmaceutical formulation including the thrombin inhibitor, or derivative, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including the other therapeutic agent in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

30. A combination product as claimed in any one of Claims 27 to 29, wherein the thrombin inhibitor is melagatran.

31. A combination product as claimed in Claim 30, wherein the derivative of melagatran is a prodrug of melagatran.

32. A combination product as claimed in Claim 31, wherein the prodrug is of the formula

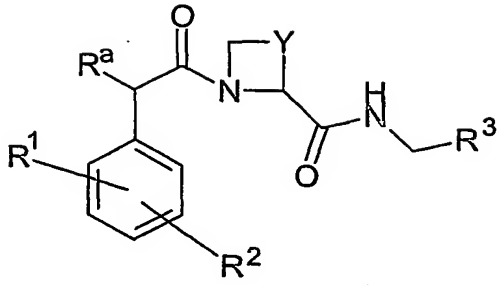
$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}(S)Aze\text{-}Pab\text{-}OH,$$

wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab.

33. A combination product as claimed in Claim 32, wherein R^1 represents methyl, ethyl or propyl.

34. A combination product as claimed in Claim 33, wherein R^1 represents ethyl.

35. A combination product as claimed in any one of Claims 27 to 29, wherein the thrombin inhibitor is of formula I,



wherein

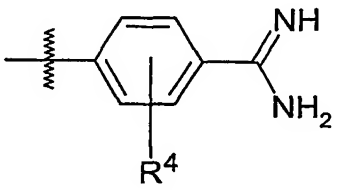
R^a represents -OH or $-CH_2OH$;

R^1 represents at least one optional halo substituent;

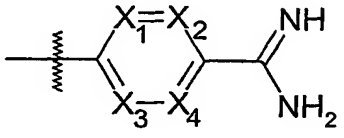
R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

Y represents $-CH_2-$ or $-(CH_2)_2-$; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i)



I(ii)

wherein

R^4 represents H or one or more fluoro substituents; and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-.

36. A combination product as claimed in Claim 35, wherein the thrombin inhibitor is:

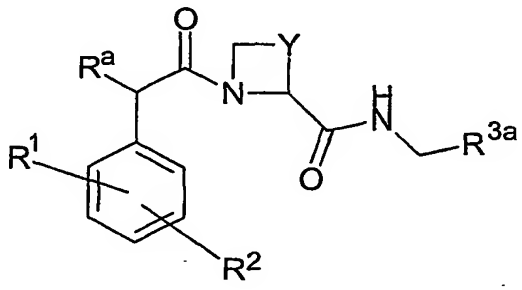
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab;

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF); or

Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab.

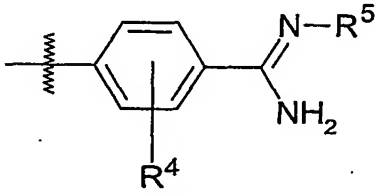
37. A combination product as claimed in Claim 35 or Claim 36, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

38. A combination product as claimed in Claim 37, wherein the prodrug is of formula Ia,

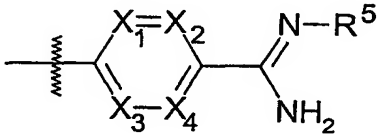


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a, R^1, R^2, Y, R^4, X_1, X_2, X_3 and X_4 are as defined in Claim 35.

39. A combination product as claimed in Claim 38, wherein the prodrug is:
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe);
Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe); or
Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe).

40. A combination product as claimed in any one of Claims 27 to 39, wherein the other therapeutic agent is a statin.

41. A combination product as claimed in Claim 40 wherein the statin is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin or rosuvastatin.

42. A pharmaceutical formulation for use in cholesterol-lowering therapy, which formulation comprises an effective amount of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof.

43. Use of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in cholesterol-lowering therapy, by administering that inhibitor, or pharmaceutically-acceptable derivative, to a patient.

44. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in cholesterol-lowering therapy.